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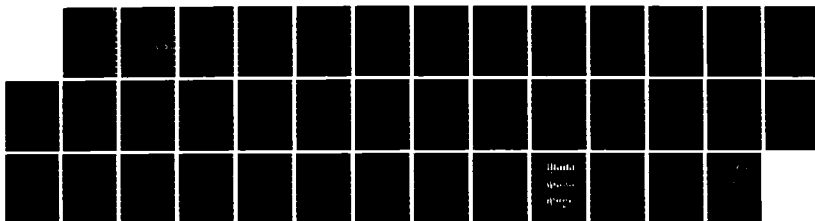
ACETAZOLAMIDE AND ADH RENIN ALDOSTERONE AND WATER
ELECTROLYTES AT 4100 M. (U) ARMY RESEARCH INST OF
ENVIRONMENTAL MEDICINE NATICK MA J R CLAYBAUGH ET AL.
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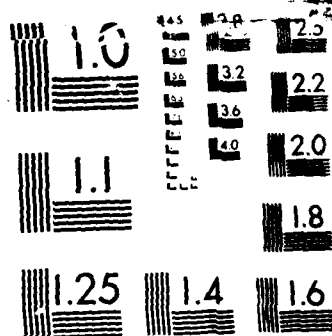
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but by day 3, the subjects were in normal water and Na balance. Both K and water balance were similar between groups at HA. Na balance was significantly reduced in the AZ group for all days at HA, probably a consequence of significantly reduced caloric intake in that group. The plasma aldosterone to renin ratio was significantly lower in the PM than AM at SL, and both AM and PM ratios were reduced at HA. Urinary ADH excretion was significantly increased on days 4 and 5 in the placebo group, but only on day 4 in the AZ group, and was significantly lower on day 5 in the AZ group. Thus AZ blunts the ADH response to HA, a possible mechanism of the AMS ameliorative actions of the drug.

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ACETAZOLAMIDE AND ADH, RENIN, ALDOSTERONE, AND WATER
AND ELECTROLYTES AT 4100 M IN MAN

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The opinions and conclusions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

ABSTRACT

Male volunteers comprised two groups, one (n=7) received acetazolamide (AZ), 150 mg twice daily; a second received placebo (n=6). These subjects were reduced to 6 and 4, respectively, because of acute mountain sickness (AMS). Morning (0700-0900 AM) and evening (2100-2200 PM) blood samples were obtained on various days, and all urine was collected. On day 4 the subjects were transported from sea level (SL) to 4100 M (HA) over a period of three hours and returned to SL on day 9. Intakes of field rations and water were measured. The subjects lived in tents. AZ resulted in a brief diuresis, natriuresis, and kaliuresis on day 1, but by day 3 the subjects were in normal water and Na balance. Both K and water balance were similar between groups at HA. Na balance was significantly reduced in the AZ group for all days at HA, probably a consequence of significantly reduced caloric intake in that group. The plasma aldosterone to renin ratio was significantly lower in the PL than AZ at SL, and both AM and PM ratios were reduced at HA. Urinary ADH excretion was significantly increased on days 4 and 5 in the placebo group, but only on day 4 in the AZ group, and was significantly lower on day 5 in the AZ group. Thus AZ blunts the ADH response to HA, a possible mechanism of the AMS ameliorative actions of the drug.

Index Terms: Renin-aldosterone circadian rhythm
Acute mountain sickness
Sodium balance
Potassium balance
Fluid balance
High altitude



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Acetazolamide (AZ) has been shown to prevent or ameliorate the symptoms of acute mountain sickness (AMS) resulting from rapid ascent to high altitudes (1,3,9,10,12,14,22). Generally it is believed that a cascade of events beginning with a loss of bicarbonate ion in the urine, resulting in an decreased alkalinity of the blood and subsequent augmented ventilation, increases arterial oxygen tension (1,3,9,10,12,22). However, it is also frequently qualified that the increased arterial oxygen may not be the mechanism whereby AZ ameliorates AMS. For instance, Gray et al (12) point out that the resultant pH changes may reduce the oxygen extraction from hemoglobin. In addition, although low atmospheric oxygen is the initial causal factor, as Houston has indicated, "oxygen uptake is the same at high altitudes as at sea level and is not changed by acclimatization" and he therefore concluded that the resultant symptoms are not from oxygen lack but secondary changes (18).

In addition to acid-base alterations, AZ is a mild diuretic. As Singh et al (31) observed, that persons predisposed to AMS suffered from antidiuresis. Moreover, the plasma volume increased in a single case of AMS while to eight asymptomatic colleagues had decreased plasma volume (28). Thus, as suggested by others (16), a possible additional mechanism of action of AZ in preventing AMS may be via its effects in altering body fluid and electrolyte balance.

In the present study, therefore, the water and electrolyte and associated hormonal responses were compared in men with and without AZ prophylaxis at the summit area of Mauna Kea, 4,100 M.

Materials and Methods

Experimental Design:

Thirteen male soldiers ranging in age from 19 to 30 years and weight from 61 to 105 kg volunteered to participate in the study after giving informed, written consent and being advised that they could withdraw from the study upon request. The men were randomly assigned to one of two groups. Acetazolamide (Diamox,[®] Upjohn Laboratories) was given to one group (n=7) in doses of 250 mg twice daily in slow-release capsules. Placebo capsules (prepared by Upjohn Laboratories) were given to the other group (n=6) twice daily.

Four days were spent at SL followed by four days at HA and then one and one-half days at SL. The subjects were housed in tents with no heating during the experiment. At SL temperatures ranged from 72 to 85°F. At HA, the temperature ranged from 20° F to 65°F. The subjects were fed Long Range Patrol rations, a freeze-dried homogenous mixture, e.g., corned beef hash, to which a measured amount of water could be added, and the contents were weighed before and after eating to determine intake measurements. In addition, candy bars and powdered orange drink were available. All food and water were ad libitum except for two hours before blood samples. Mild exercise was also allowed.

The subjects reported to the SL study area (Tripler Army Medical Center, Oahu, Hawaii, approximately 200 M) at 0700 on day 1 and voided their bladders, and urine collections were begun. At 1700 on day 1 placebo or acetazolamide (AZ) administration was begun. On day 4 after morning sampling the subjects and staff were taken by bus to a helicopter field and flown to the island of Hawaii, landing at 1900 M elevation. They were then driven by

truck to 4,100 M at the summit area of Mauna Kea. The total time of ascent from Tripler to Mauna Kea was three hours. At noon on day 8 descent was begun, but on arrival at the 1,900 M level, a four-hour delay was incurred because of helicopter mechanical problems. Unfortunately, during this period water was not available and only snacks could be eaten, which may have affected the total food and water consumption for that day. The staff and subjects arrived on Oahu (SL) at about 1900.

Sampling Procedures:

Since diurnal rhythms affect several of the parameters studied, both morning (0700-0800) and evening (2100-2200) venous blood samples were taken on various days, and statistical comparisons were made accordingly. At each blood sampling time, heart rate (arterial pulse), blood pressure (sphygmomanometry) and body temperature (oral) were recorded. The subjects were seated for about 15 minutes before each blood drawing. Because of venous constriction resulting from the high altitude and cold, blood samples could not always be obtained without stasis. However, this was attempted and most often was achieved. The blood sampling days and morning and evening designation are indicated on the tables.

Twenty-four hour urine collections were begun at 0700 or corrected for time for slight deviations due to blood sampling not exceeding 30 minutes. The collections were made four times daily.

Urine and blood samples were aliquoted and measured immediately and kept on ice for transport to a laboratory at 1900 M for final processing or freezing. Blood samples were immediately transported and urine was transported within 12 hours.

Standard Laboratory Procedures:

Urinary sodium and potassium were measured by flame photometry with lithium as the internal standard (Instrument Laboratories Model 343). Urine and plasma osmolality was determined by a freezing point depression osmometer (Fiske Model 330D). Serum creatinine was determined by an autoanalyzer (Technicon Auto-Analyzer SMAC). Hematocrit was determined by duplicate analyses of centrifuged microcapillary tubes (IEC).

Hormone Assays: Urinary antidiuretic hormone (ADH) concentration was determined by radioimmunoassay (RIA) of unextracted urine as described previously (5). The antisera employed in the RIA was not affected by the presence of urea, and only one peak of immunologically active material was eluted from urine after Sephadex G-25 chromatography (6). The between-assay and within-assay coefficients of variability (CV) were 13.9 and 12.7%, respectively. Plasma ADH concentration was determined as previously described (7) with extraction by C_{18} cartridges (SepPak, Waters). The between and within-assay CV were 14.5 and 9.8%. Plasma cortisol was determined by use of a RIA kit (Clinical Assays, Cambridge, MA), as was plasma aldosterone (Radioassay System[®]). The between and within CV for these three assays were 11.8 and 4.5%, 9 and 4%, respectively. Plasma renin activity was determined by use of a RIA kit (New England Nuclear) with between and within CV of 12.9 and 11.0%, respectively. The plasma prolactin concentration was determined with a RIA kit (Clinical Assays) with between and within CV of 10.9 and 9.8%.

Symptomatology and Statistics: A standardized test, the environmental symptoms questionnaire, or ESQ (29) was given twice daily, once at 0700 and once at 1900. On the day of ascent, another was given at 2100. Since these

data were not normally distributed, a Wilcoxon's signed rank test (33) was used to assess statistical significance.

The plasma data was analyzed by a two-way analysis of variance on all samples. The urine data was analyzed similarly, but only for the data from day 3 to the end. This was done because the initial variability caused by the AZ treatment prior to the ascent indicated significant differences, e.g., in urine flow, that were not of interest in the response to HA. All data are shown. The differences between individual means were determined by post-hoc analysis with the Duncan's Multiple Range Test (32). The 0.05 level of probability was considered statistically significant. The regression analyses and comparison of slopes were done by t-test as described by Zar (36).

Results

There were tendencies for AZ to lessen the overall score of the ESQ test, especially on the day of ascent. Similarly, headache symptoms seemed to be reduced by AZ prophylaxis, and nausea showed no striking differences. Although HA exposure produced significant symptom changes, no differences between groups were significant. This is probably due to the small numbers which were reduced to six in the AZ group and four in the placebo group. The subject that dropped out of the AZ group had severe headache, stomach cramps, and anorexia (< 300 calories/day at HA until evacuated on day 6). The two subjects evacuated on day 6 from the placebo group had severe headache. Their data are not included in any of the analysis because of incompleteness.

Ascent to high altitude produced a similar degree of hemoconcentration in both groups. Hematocrit was significantly increased ($P < 0.01$) in both

groups by the morning after ascent and returned to sea level values the evening of the day of return (Table 1). On the day of descent the drugs were discontinued, and this may have resulted in the significant decrease in hematocrit compared to pre-ascent values after a day at SL in the AZ group. The change was small but may represent the degree of dehydration which was slight and not significant between groups before ascent. In addition to the hemoconcentration, there was evidence of water dehydration. Mean plasma osmolality was generally higher in the AZ group and statistically significant on the evening of ascent ($P < 0.01$) and after return to SL for 24 hours ($P < 0.05$, Table 1). The difference between groups in plasma osmolality is not reflected in the plasma concentrations of either sodium or potassium. Although sodium increased in both groups on the first day at altitude, potassium was unchanged until return to SL when it decreased significantly. In general, the plasma potassium concentration was lower in the AZ group, significant on the morning of day 7, and after cessation of drug administration on the morning of day 10.

The cardiovascular responses of the two groups to high altitude were similar (Table 2). Both groups showed similar increase in heart rate on the evening of the day of ascent, which was maintained during the high altitude exposure and gradually returned to SL control values by the morning of day 10 after 36 hours at SL. On the afternoon (PM) day 3 and the morning (AM) of day 4, the heart rate was higher in the AZ group than the placebo group ($P < 0.05$), but otherwise the groups were similar. Systolic and diastolic blood pressures were not different between groups at SL and only on the evening after ascent was the diastolic pressure in the AZ group significantly higher than the placebo group. There was a tendency for systolic and diastolic

pressures to be elevated at high altitude, but this was significant only in the AZ group.

Oral temperatures (Table 2) dropped similarly in both groups on the evening after ascent ($P < 0.01$), showed some recovery, and then were low again on the last morning, day 8, at altitude ($P < 0.01$). Temperatures were normal after return to sea level.

High altitude resulted in a significant increase in the evening plasma concentration of ADH ($P < 0.05$) only in the placebo group (Table 3). The AZ group demonstrated no changes. Although the mean values are the same for day 4 PM and day 7 PM in the placebo group, these are rounded off values, and day 4 PM missed statistical significance.

The PRA in both groups slowly increased reaching significance on the seventh day and generally remained elevated (Table 3). In the AZ group a greater response is seen, achieving PRA values of about two times the placebo group. Similarly, plasma aldosterone concentration (PAC) was not immediately affected by the rapid ascent to high altitude in either group. In both groups the PAC became significantly higher than pre-ascent control values only after return to SL. The AZ group occasionally had significantly higher PAC values than the placebo group at both HA and SL. Further evaluation of these data show that the PRA-PAC relationship changes as a function of time of day at SL (Fig. 1, $P < 0.01$). High altitude exposure resulted in a suppression of this relationship during morning ($P < 0.001$) and evening ($P < 0.01$) samples. Correlations comparing AZ and placebo indicated more variability in the PAC-PRA relationship in the AZ groups, but no differences in slopes between the two groups at the various times could be determined.

Plasma cortisol concentrations were significantly elevated on the evening of the day of ascent in both groups with no difference between groups (Table 3). Similarly, plasma prolactin was not different between groups and showed no response to HA (Table 3).

Acetazolamide resulted in a diuresis ($P < 0.01$) on the first day and concurrently reduced sensible water balance (water intake minus urine output, Figure 2). These statistics are not indicated on Figure 2 since other comparisons are as stated in the methods section. By the third day the water balances between the two groups were similar, and there were no subsequent differences between them. The AZ group had a reduced sensible water balance on the first day ($P < 0.01$) at high altitude and continued a reduced balance on the second day ($P < 0.05$). The placebo group roughly paralleled this pattern but was not different from its control value. The reduction in water balance during these first two days at high altitude appears to be a consequence of maintained urine output and significantly reduced water intake. Both the AZ and placebo groups consumed approximately 1 liter less ($P < 0.01$) than at SL the day before (Figure 2). Although the placebo group improved somewhat the second day, the AZ group remained at a low fluid intake ($P < 0.01$) and fluid balance. The reduction in fluid intake on day 8 ($P < 0.01$) in both groups was probably due to the helicopter failure mentioned in the methods section.

Sodium balance was also reduced during the first day in the AZ group ($P < 0.01$, statistics not shown on Figure 2), but returned to values similar to those of the placebo group by day 3. Both groups showed a significant negative sodium balance on the day of ascent to high altitude ($P < 0.01$, AZ, and $P < 0.05$ placebo). However, on day 5 the placebo group returned to

sodium balances comparable to SL, and the AZ group remained significantly lower for the entire HA exposure. This reduced sodium balance in the AZ group was partially due to reduced sodium intake evident on all days at HA. Moreover, the reduction in sodium intake was significantly lower on days 5 ($P < 0.05$) and 7 ($P < 0.01$) than in the placebo group. Sodium excretion was significantly less in the AZ group on days 3 ($P < 0.05$), 5 ($P < 0.05$), and 7 ($P < 0.05$). There was a gradual decrease in sodium excretion in both groups as the experiment progressed. This was evident on days 7 ($P < 0.05$), 8 ($P < 0.01$), and 9 ($P < 0.01$) in the AZ group and days 8 ($P < 0.01$) and 9 ($P < 0.01$) in the placebo group. The reduced sodium intake on these days would appear to be a consequence of eating less food as judged by caloric intake (Figure 3).

Potassium balance (Figure 2) was negative on the first day of AZ treatment similar to water and sodium balance, but remained lower than the placebo group through day 3 at sea level ($P < 0.05$). Ascent to HA resulted in a reduction in potassium balance in the placebo group ($P < 0.05$), compared to day 3, but this was not sustained on subsequent days at HA. There was a reduction in potassium balance on the day of descent in both groups ($P < 0.05$ AZ, and $P < 0.01$ placebo). However, similar to water balance and sodium balance, this may have been partially affected by the transportation difficulties (see methods) resulting in decreased water and food consumption.

The caloric intake was immediately reduced in both the placebo and AZ groups at HA (Figure 3), but was reduced more in the AZ group evident on days 3 ($P < 0.01$) and 5 ($P < 0.05$).

To summarize the balance responses, after three days of AZ this group was similar to the placebo group in both water and sodium balance, but

significantly lower in potassium balance. The day of ascent resulted in reduced balances of water, sodium and potassium, but water and potassium balance recovered, and sodium balance recovered only in the placebo group. It is difficult to interpret day 8 because of the transportation problems, but reduced balances were observed in both groups for water, sodium, and potassium. The differences, however, between the reduced balances during ascent and descent are that on the day of ascent, sodium and potassium intakes were comparable to sea level control values, and the reduced water intake on the day of descent resulted in an appropriate response to by decreased urine flow.

The low excretion rates of sodium and potassium were paralleled by low osmotic clearances in the AZ group (data not shown). Since there were similar between-group urine flow rates, the AZ group produced a more dilute urine (Figure 4). Thus on days 6 and 7, the urine osmolality was more dilute in the AZ group than the placebo group ($P < 0.05$). Despite discontinuance of the AZ and return to sea level, the final day's urine was also more dilute in the AZ group ($P < 0.01$). The responses were essentially opposite, with the AZ group tending to decrease urine osmolality between day 3 through day 7 (day 6, $P < 0.05$, day 7, $P < 0.05$) and the placebo group tending to increase urine osmolality, resulting in a statistically significant interaction ($P < 0.025$). The increases in the latter group were, however, not significant.

During the first two days of AZ treatment, the slightly less concentrated urine and increased flow probably resulted in a volume depletion which stimulated ADH on day 1 (Figure 5). However, this response was temporary and by day 2 and 3, urinary ADH was similar between groups. At

high altitude the average urine ADH excretion rate was usually higher in the placebo group. The greatest difference occurred on day 5 ($P < 0.05$). The urinary ADH excretion rate was increased in the AZ group after high altitude exposure on day 4 ($P < 0.05$). In contrast, both days 4 ($P < 0.05$) and 5 ($P < 0.05$) were significantly greater than day 3 in the placebo group.

Discussion

There have been several possible mechanisms proposed that may be involved in development of the symptoms of AMS. One approach to the problem has been to administer AZ and observe differences in responses to untreated subjects. In most recent studies AZ has demonstrated an amelioration of symptoms. Most studies have focused on the ventilatory and acid-base responses in control and AZ treated subjects (1,3,9,10,12,22,34). As a secondary issue in some studies it has been reported that AZ prophylaxis does not affect urine excretion rates at high altitude (2,22), although it may produce a slight lowering of plasma potassium, but still within normal range (3). Frayser et al (11) approached the problem in a manner similar to the present study, focusing on the renin and aldosterone hormone systems and the urinary excretion and plasma concentrations of sodium and potassium. The results of the present study are in general agreement with these reports.

There was not a statistically significant effect of AZ on the symptomatology of AMS. Other studies demonstrating significant effects have used larger numbers of subjects, the least being ten men in each group (1). Our results, albeit only suggestive, are in agreement with these previous reports.

Several years ago Singh et al (32) suggested that the increased plasma concentration of ADH he observed in HA pulmonary edema susceptible subjects at HA, may be causally related to AMS. This theory has had difficulty in acceptance because of the inconsistency of reported values of ADH at altitude and during AMS. There appears, however, to be a pattern in the diverse responses of ADH to hypoxia. Thus, with a slow ascent of 1,500 M per day as the maximum rate of climb, altitudes of 6,000 M will not result in elevated urinary excretion of ADH (15). With rapid ascent there is a dependence on the hypoxia level, such that with rapid increases in altitude of 2,000 M (25) or with moderate levels of hypoxia for a short duration, plasma ADH is reduced (4). However, with rapid decompression to equivalent pressures of 5,100 M, plasma ADH is increased (17). Furthermore, the ADH excreted during the first day at altitudes over approximately 3,500 M is probably always increased if the decompression is rapid (7). Also, this increase in ADH appears to be dose-dependent on the level of hypoxia (7). Thus, the ADH response correlates well with the conditions necessary for the appearance of AMS.

Increased plasma ADH concentration with AMS symptoms, with the exception of high altitude pulmonary edema-prone subjects, is frequently not observed (13). However, the urinary excretion of the hormone can be greatly elevated, but only for a brief two to three hour period (7). It is not likely that enough body fluid conservation could occur during such a brief interval to bring about the volume expansion that has been reported with AMS (28). However, the observation that the increases in urinary ADH precede headache and wane during the continuation of the headache (7) indicates that possibly ADH is initiating the effect. Wang et al (36) have demonstrated

that hypoxia stimulates ADH release into the CSF concomitant with an increased plasma ADH, but after 30 minutes of recovery, plasma ADH returned to normal and CSF ADH remained elevated and similar to hypoxia conditions. This is of interest because ADH in the CSF has been reported to increase brain water (27). Thus, increased urinary or plasma ADH during hypoxic stress may be paralleled by increases in the release of the hormone to the CSF or other central sites of action.

In this regard, the results of the present study indicate that if ADH is involved in the cause of AMS, AZ therapy is causing the desired effect, i.e., a reduction of the initial surge of ADH occurring during the first hours at high altitude. Of interest are the recent reports that dexamethasone, a potent glucocorticoid, prevents AMS (19), and that increased endogenous corticosteroids essentially eliminate the ADH response to hypoxia in dogs (26). Thus part of the mechanism of dexamethasone may also be via ADH inhibition at high altitude. Indeed, its administration resulted in increased urine output compared to controls (19). Although the mechanisms of ADH inhibition during AZ therapy may be via the relatively increased ventilation, subsequent increased thoracic blood volume, and baroreceptor inhibition of ADH release, the mechanism of cortisol on ADH inhibition is not clear. According to the present study, the only suggestive inhibition of plasma ADH by AZ occurred at night. Although the subjects were not sleeping, the late time of the sampling, 2100, may have coincided with increased episodic breathing in the placebo group which has been reported to be decreased by AZ (34). Thus, the exaggerated hypoventilation during sleep would be expected to increase ADH, and AZ, by promoting more regular breathing, would tend to inhibit its release.

In spite of the increased urinary ADH and occasionally increased plasma ADH concentration, the urine flow rates were similar between the two groups as others have reported previously (2,11,22). The mechanisms, however, appear to be different. The creatinine clearances were not different at high altitude, but the urine osmolalities were greater in the placebo group than in the AZ group, corresponding with the relatively higher ADH levels in the placebo group. Despite the more dilute urine, however, the AZ group maintained similar urine flows to the controls. It would appear that the AZ group, as a consequence of the initial volume reduction and electrolyte loss, was generally secreting more renin which became significant during the latter portion of high altitude exposure. Similarly, plasma aldosterone levels were generally higher. This apparently resulted in more avid sodium retention and possibly a reduced renal distal tubular delivery. Thus despite lower ADH levels, as detected in the 24 hour urine excretion, and lower urine osmolality, the urine flows were similar between the two groups. Although a direct comparison was not possible to the study by Frayser et al (11), the third and fifth days at 17,500 ft in their study, after this group had had a staged ascent, were characterized by greater sodium excretion than in AZ premedicated subjects at day 4 at the same altitude. This response is similar to that observed in the present study.

There was an apparent affect of acetazolamide on appetite evidenced by reduced caloric intake. The rations were available ad libitum for the most part. Probably as a result of this decreased intake of food, both groups showed reduced intake and reduced urinary excretion of sodium and potassium. Overall, this effect was greater in the AZ group, which resulted in a significantly reduced sodium balance that was negative for the entire high

altitude exposure. The placebo group, however, returned to normal sodium balance after the day of ascent. The caloric, sodium, and potassium intakes were not different between the two groups at SL. Thus the effect of AZ per se on appetite is not supported by our data, but seems to be precipitated by ascent to high altitude. Forward et al (10) characterized gastrointestinal symptoms as mild, moderate, or severe distinguished by anorexia, nausea, and vomiting, respectively. In their study, AZ treatment produced significantly greater symptomatology on day 1 at high altitude (12,800 ft) than in the control subjects, and most of the symptomatology was due to anorexia. Upon cessation of the drug after day 2 in their study, the anorexia disappeared. In our study the drug was administered for four days at HA which may have prolonged the effects.

The water balance was indistinguishable between the two groups after 48 hours of AZ treatment at sea level. Upon ascent to HA there was reduced water intake by both groups which recovered completely by the fourth day at HA. The AZ group was not different from the placebo group at any period. Of interest is the maintained urine flow on the day of ascent opposed by a reduced fluid intake. This resulted in decreased sensible water balance, which would tend to decrease body water as observed by others (21). The mechanism of the decreased thirst drive at HA has been extensively investigated in the rat (20). These studies indicate that the osmotic threshold for thirst is increased during hypoxia independent of ADH, renin, body temperature, or volume status. The investigators concluded, therefore, that "the mechanism resides beyond the central integration of osmotic and nonosmotic information, or at the osmotic sensing mechanism itself."

In spite of the decreased water balance, there were no significant increases in plasma osmolality at HA. Assuming no short-term transient increases in plasma osmolality, the stimulus for ADH release in the control group was probably due to either the body fluid volume reduction or the direct effects of hypoxia at the chemoreceptor (30). Insofar as the high pressure system receptors could be involved, there were no decreases in systolic or diastolic pressures or heart rate that would account for the increased ADH observed in the control group. The results cannot discount a possible role of the low pressure receptors in the cardiac atria in the stimulation of ADH. However, with a chemoreceptor and/or atrial receptor mechanism, another difficulty lies in understanding the means by which the ADH release is inhibited after 24 to 48 hours at HA. Little information is available on the long-term effects of reduced volume or chemoreceptor stimulation on ADH control.

Higher levels of renin and aldosterone during the early morning compared to evening have been reported previously (23). Only recently, however, has it been proposed that aldosterone rhythmic control at night is influenced very little by the renin-angiotensin system, but during the daytime this influence of the renin-angiotensin system is greater (35). The present study supports these findings. That is, the plasma aldosterone concurrent with plasma renin activity was lower in the evening at sea level. Presumably because of the decreased volume status brought about by the AZ administration, renin was stimulated. Thus in all of the experimental conditions, a range of renin, i.e., low for the controls and higher for the AZ group, was achieved. Consequently, slopes relating the aldosterone response (ordinate) to plasma renin activity (abscissa) could be constructed

(fig. 1). The relationship between aldosterone and PRA was not affected by HA as mentioned in the results. The results of the present study show that HA further suppresses this aldosterone response to renin such that in the evening the adrenal glands seemed essentially unresponsive to even high levels of renin.

The present study does not add to the understanding of the mechanism of the decreased renin stimulation of aldosterone at HA. Plasma levels of angiotensin converting enzyme have been reported to be lower at HA (24), and the conclusion is that angiotenin II is therefore lowered. However, in recent studies on normal human subjects, a similar situation of decreased aldosterone responsiveness to renin was observed with acute hypoxia in spite of unchanged plasma angiotensin converting enzyme levels (8). Thus the mechanism of decreased aldosterone responsiveness to renin at HA is still unclear.

In summary, the present study has confirmed that urinary excretion of ADH is increased during the first 24 hours after acute ascent to HA. Previous studies had been conducted in hypobaric chambers and the response appears to occur during the more rigorous field conditions of this study, including subfreezing overnight temperatures. The relationship of ADH to AMS is still theoretical, but it is interesting to note that AZ prophylactic therapy reduces this surge in ADH during the first 24 hours at HA. After the sea level equilibration period, sodium and water balances were similar between AZ and placebo treated subjects but potassium balance was still lower in the AZ group. At HA, however, only sodium balance was consistently lower in the AZ group, which probably resulted in significantly higher plasma renin and aldosterone levels in that group. AZ had no effect on the

renin-aldosterone relationship; however, at sea level a greater responsiveness of aldosterone to renin was noticed in the morning compared to evening. High altitude reduced the aldosterone response to renin in both AM and PM samples. All subjects showed a decreased caloric intake, but the AZ group was apparently more anorectic. It would seem advisable to discontinue AZ therapy after two days at high altitude in order to improve appetite and sodium balance.

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TABLE 2: Cardiovascular and Oral Temperature Responses During Morning and Night at Sea Level and High Altitude

	RX	Sea Level					High Altitude					Sea Level				
		3 AM ¹	3 PM	4 AM	4 PM	5 AM	7 AM	7 PM	8 AM	8 PM	10 AM	3 AM	3 PM	4 AM	4 PM	5 AM
HR	P	63.0±1.7	60.0±4.9	61.5±3.8	82.0±7.7 ⁺⁺	99.5±7.6 ⁺⁺	78.0±6.9 ⁺	84.0±1.4 ⁺⁺	84.0±7.3 ⁺⁺	76.5±4.5 ⁺	69.0±3.9					
	A7	68.3±4.5	75.0±5.7 [*]	75.0±5.0	90.0±4.9 ⁺	85.3±4.6	97.0±4.6	92.3±2.5 ⁺⁺	92.0±3.4 ⁺⁺	84.0±4.1	77.0±1.8					
SBP	P	117±6	128±6	120±7	140±4	130±3	130±5	130±12	121±6	111±7	115±6					
	A7	125±4	122±5	120±4	138±5 ⁺	130±4	136±4 ⁺	134±5	128±3	122±7	118±4					
DBP	P	73±3	71±6	73±2	71±8	78±6	86±4	79±11	78±7	79±5	78±3					
	A7	85±4	81±5	79±2	85±3 [*]	82±6	96±4 ⁺⁺	90±4	90±4	79±3	78±3					
BT	P	98.1±0.1	98.9±0.2	98.3±0.3	96.7±0.3 ⁺⁺	97.5±0.6	97.4±0.1 ⁺	98.0±0.2	96.7±0.4 ⁺⁺	98.3±0.1	97.4±0.2					
	A7	98.4±0.1	98.6±0.1	98.1±0.2	96.6±0.3 ⁺⁺	97.1±0.4 ⁺⁺	97.6±0.3	98.5±0.3	96.6±0.2 ⁺⁺	98.5±0.1	98.2±0.3					

HR = heart rate (b/min), SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg), BT = body temperature determined orally (°C). Other symbols and abbreviations are as described in Table 1.

TABLE 3: Plasma Concentrations of Hormones During Morning and Night at Sea Level and High Altitude

	<u>Sea Level</u>		<u>High Altitude</u>						<u>Sea Level</u>	
	RX	3 AM	4 AM	4 PM	5 AM	7 AM	7 PM	8 AM	8 PM	10 AM
P _{ADH}	P	1.5±0.5	1.3±0.2	1.6±0.4	2.7±1.0	1.0±0.4	1.8±0.4	2.7±1.3 ⁺	1.6±0.9	1.3±0.2
	AZ	1.9±0.5	2.1±0.4	1.5±0.1	1.5±0.6	1.7±0.7	1.5±0.3	1.2±0.2 [*]	0.9±0.2	1.0±0.2
P _{RA}	P	0.6±0.1	0.3±0.1	0.5±0.1	1.8±0.4	1.6±0.4	1.9±0.5	3.7±1.0 ⁺	2.1±0.7	2.6±1.0 ⁺
	AZ	1.3±0.2	1.7±0.5	1.6±0.3	2.5±0.3	2.4±0.3	3.7±0.5 ^{**}	4.9±1.3 ^{***}	4.2±0.7 ^{***}	6.0±0.9 ^{***}
P _{PAC}	P	55±17	12±2	45±9	32±13	32±8	67±30	27±10	52±15	72±16 ⁺
	AZ	135±36 ^{**}	58±23	93±15	48±11	83±20 [*]	103±27	40±10	95±25	140±23 ^{**}
P _{CORT}	P	10.2±1.3	1.7±0.4	9.1±0.9	11.6±3.4 ⁺⁺	11.4±2.3	12.5±4.0	6.6±2.3	10.6±0.6	8.6±1.8
	AZ	10.3±1.9	1.9±0.1	8.7±0.8	6.2±2.2 ⁺	9.1±1.4	4.5±0.8	8.7±2.3	10.7±1.2	8.7±2.3
P _{PROL}	P	11.0±2.0	17.4±4.4	9.8±1.1	22.9±7.7	10.9±0.4	12.6±1.3	16.3±1.5	11.2±1.6	16.7±1.8
	AZ	15.5±2.8	12.2±1.3	12.6±2.3	17.9±3.2	11.4±0.2	11.8±2.4	14.1±1.7	13.1±3.1	17.7±4.5
									15.0±3.4	15.1±3.1

P_{ADH} = plasma ADH concentration (ng/ml), P_{RA} = plasma renin activity (ng/ml/hr), P_{PAC} = plasma parathyroid hormone (pg/ml), P_{CORT} = plasma cortisol concentration (ng/ml), P_{PROL} = plasma prolactin concentration (ng/ml).

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Figure 1: Correlations (r) of plasma aldosterone concentration and renin activity as a function of time of day (AM - morning, PM - evening) and altitude. Both AM and PM values demonstrated significant correlations at sea level but not at high altitude. The sea level AM slope of 0.051 was significantly steeper than the PM slope of 0.017 ($P < 0.01$). At high altitude this difference was not significant. Both AM ($P < 0.001$) and PM ($P < 0.01$) slopes at sea level were greater than corresponding slopes at high altitude (AM slope = 0.011, PM slope = 0.003).

Figure 2: Fluid, sodium, and potassium intakes, urinary excretion rates, and balances. The shaded period on days 1 and 2, designated EP (equilibration period), was not included in the statistical analysis. SL = sea level control day (days 3 and 9). A = day of ascent. HA = period of high altitude exposure. D = day of descent. * = $P < 0.05$ and ** = $P < 0.01$ compared to day 3, SL control. + = $P < 0.05$ and ++ = $P < 0.01$ between groups. P = placebo group, AZ = acetazolamide group. Intake is designated by the total height of the open and cross-hatched bars, and urine excretion by the total length of the shaded bar and cross-hatched bars. The balance is the length of the cross-hatched bars, positive above the zero line and negative below.

Figure 3: Caloric intake. The periods are designated by the same abbreviations as in Figure 2. Significant changes are designated as in Figure 2.

Figure 4: Urine osmolality. Abbreviations and symbols are as described in Figure 2.

Figure 5: Urinary ADH excretion, mU/day. Abbreviations and symbols are as described in Figure 2.

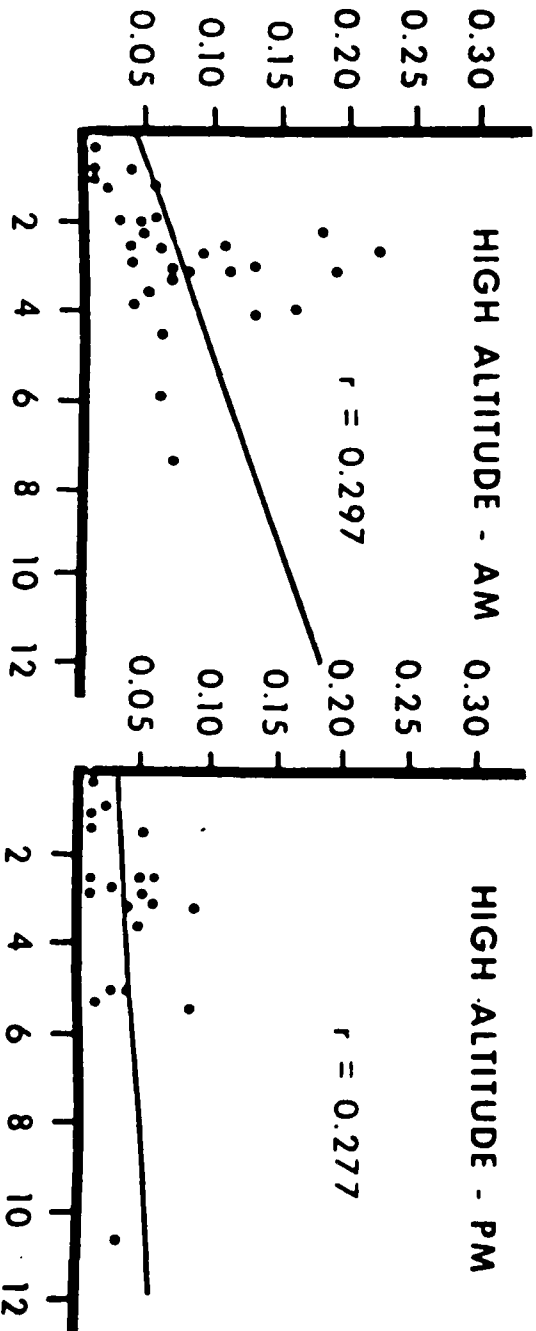
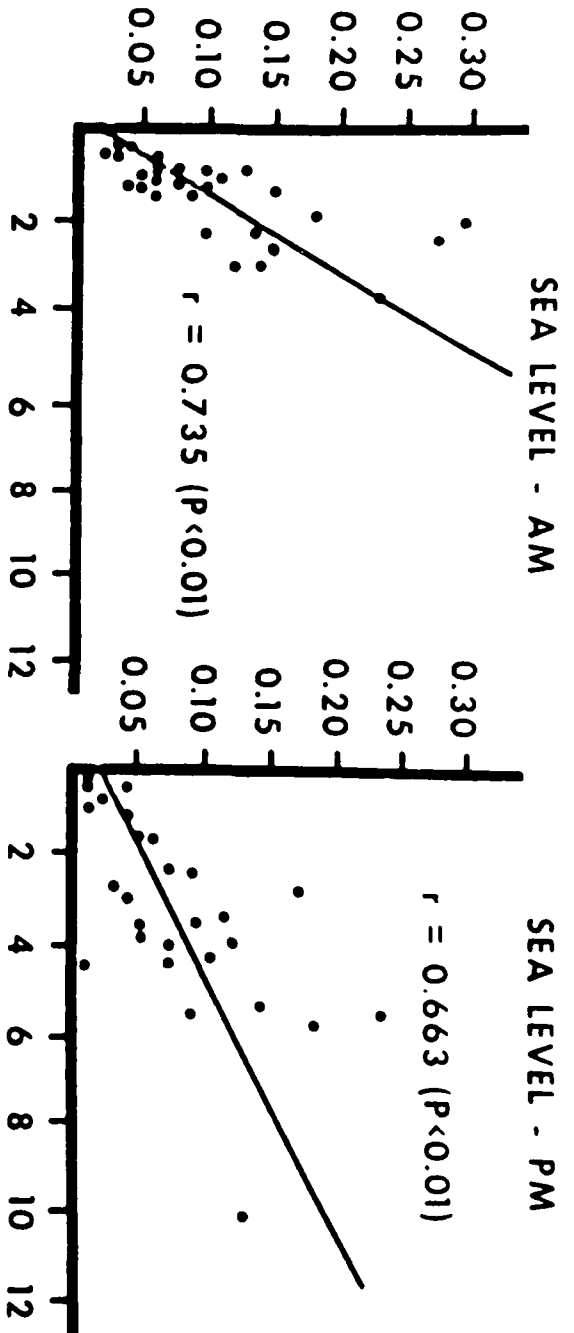
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Fig 1

PLASMA ALDOSTERONE CONCENTRATION (ng/ml)



PLASMA RENIN ACTIVITY ($\text{ng} \cdot \text{ml}^{-1} \cdot \text{hr}^{-1}$)

Fig 2

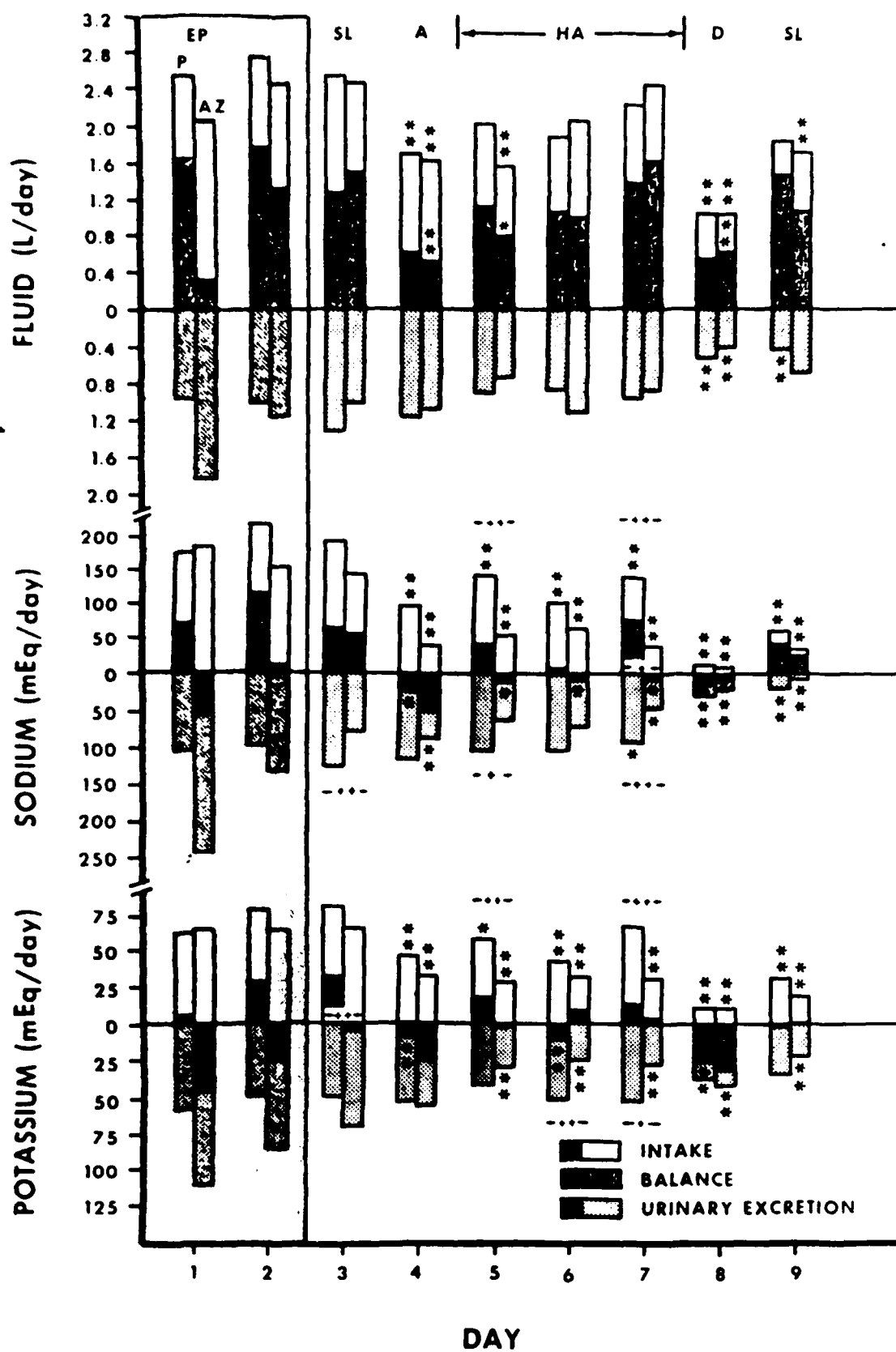


Fig 3

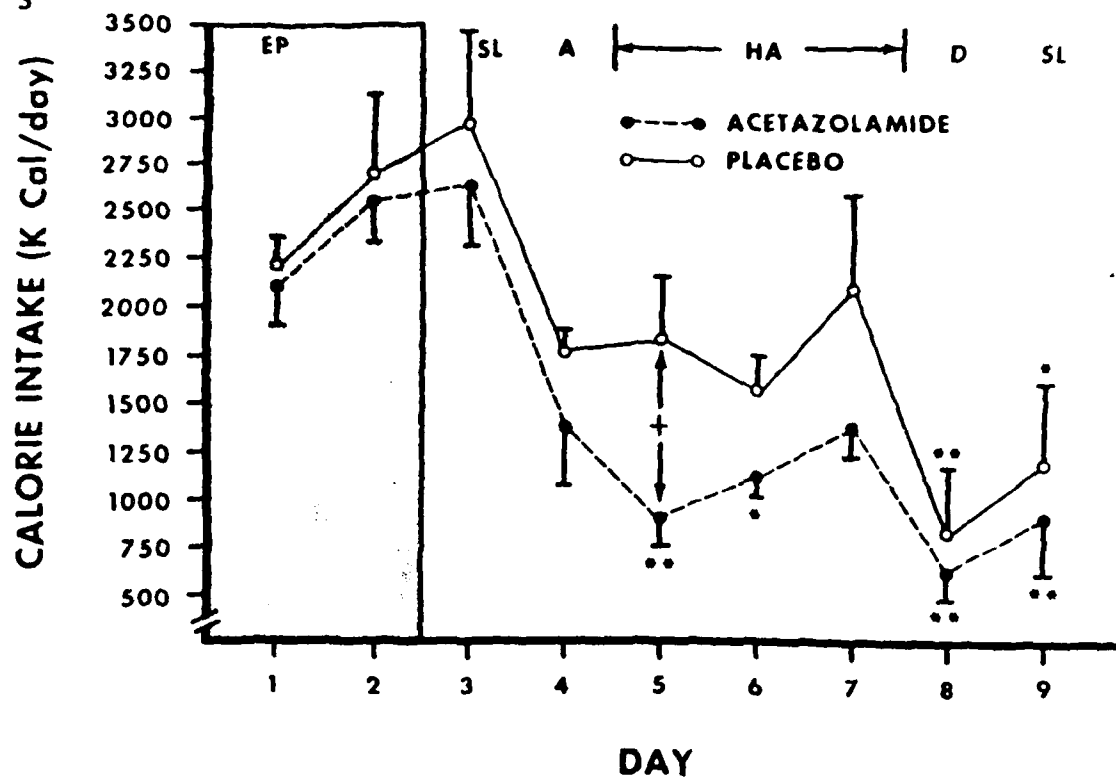


Fig 4

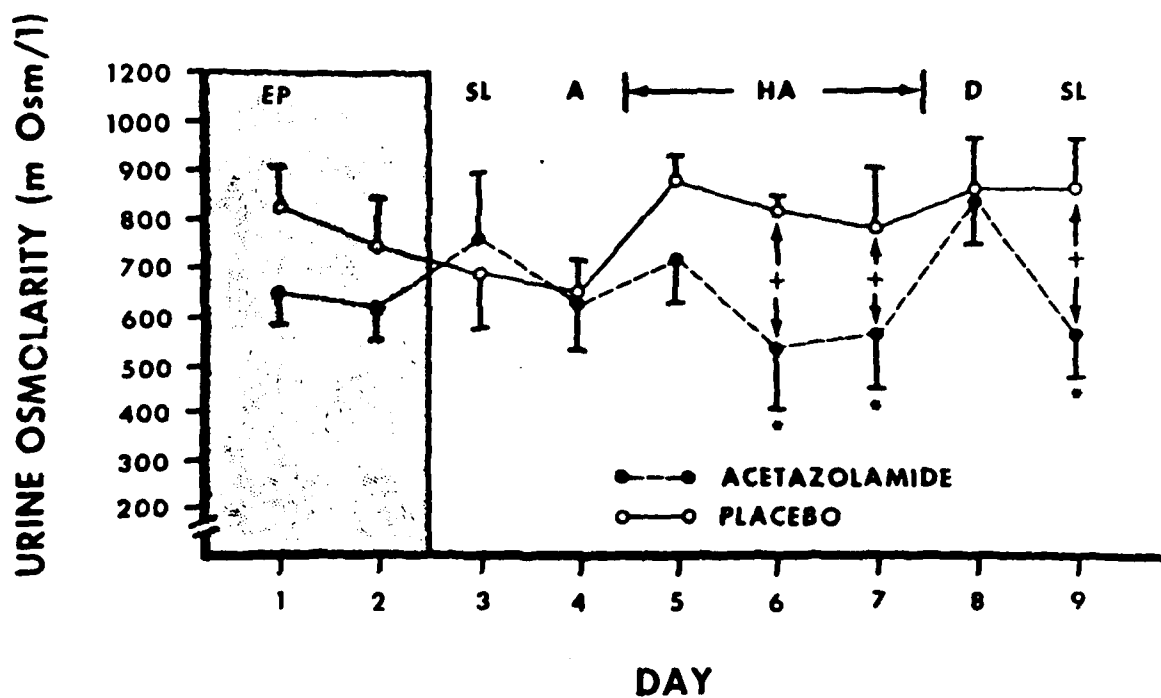
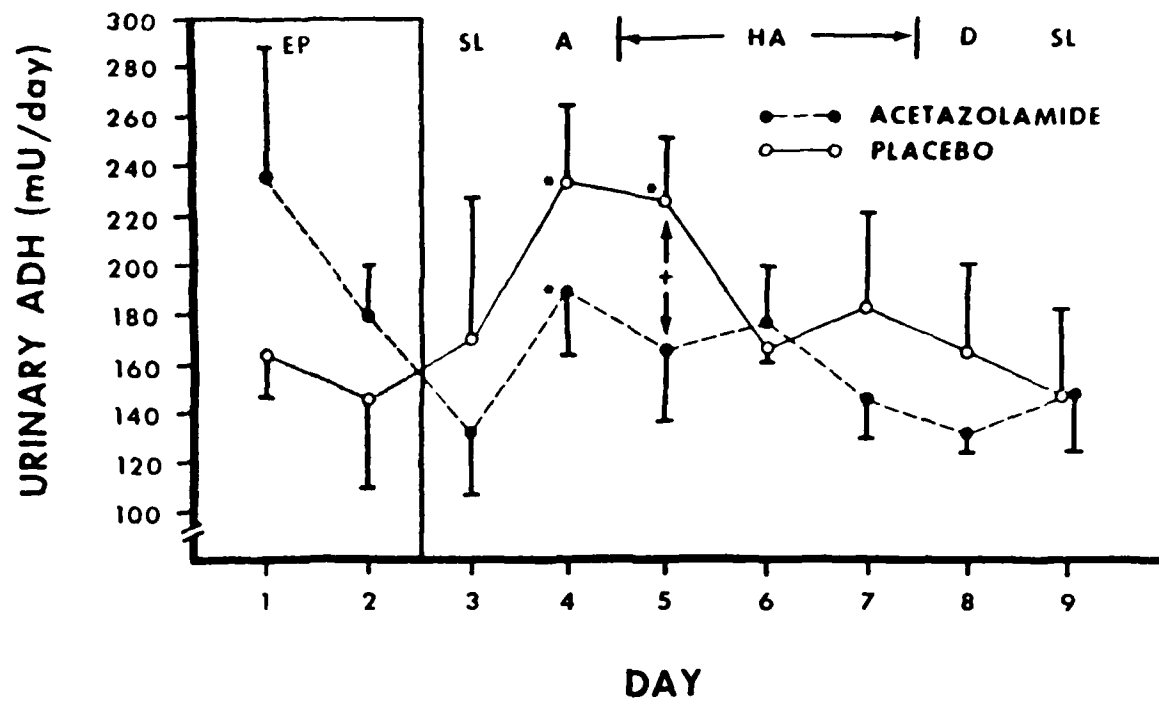


Fig 5



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